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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,827	01/31/2005	Simona Jevsevar	LB/G-32992A/LEK	2050

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,827	JEVSEVAR ET AL.	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-22 and 24-26* is/are pending in the application.

4a) Of the above claim(s) *24* is/are withdrawn from consideration.

5)☒ Claim(s) *1,6,8-11,13,14 and 20-22* is/are allowed.

6)☒ Claim(s) *2-5, 7, 15-19 and 26* is/are rejected.

7)☒ Claim(s) *25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *seq. alignment*.

DETAILED ACTION

Response to Amendment

Applicant's amendments of the specification and the claims filed 10 November 2008 have been entered.

Claims 12 and 23 are cancelled. Claims 1-11, 13-22 and 24-26 are pending. Claim 24 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Claims 1-11, 13-22, 25 and 26 are under examination.

Sequence Rules Compliance

Applicant has amended the specification to add sequence identifiers to the sequences recited in the specification, e.g., the sequences in Fig. 2. In addition, Applicant has amended the Sequence Listing to include sequences originally disclosed in the application, but not previously included in the Sequence Listing. The instant application is now in compliance with the sequence rules, 37 CFR 1.821-1.825.

Claim Rejections Withdrawn

The rejection of claim 2 under 35 U.S.C. 112, second paragraph, as being indefinite for referring nucleotide positions without referring a SEQ ID, is withdrawn in response to Applicant's amendment of the claim to recite that the modification is with respect to a native sequence coding for hG-CSF of SEQ ID NO: 3.

The rejections of claim 21 under 35 U.S.C. 112, second paragraph, as being indefinite for lacking antecedent basis for the limitation "IPTG", and for reciting the

relative terms "at least about" and "less than about", are withdrawn in response to Applicant's argument that "IPTG" is a new limitation being added in the claim and does not need antecedent basis, and Applicant's amendment of the claim to change the relative terms.

The objections to claims 2, 14, 16 and 17 for various typographical errors are withdrawn in response to Applicant's amendment of the claims.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-5, 7, 15-19 and 26 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, for reasons set forth in the previous office action.

Applicant argues that the specification fully describes how to optimize the native gene coding for hG-CSF, defined by SEQ ID NO: 3, by making modifications to particular segments of the gene, as taught on pages 8-10 of the specification. Applicant argues that the specification has provided an example of how to make a particular optimized gene, Fopt5, described by SEQ ID NO: 1, and it is believed a person of skill in the art could readily apply the concepts described in the specification to further optimize the native gene (SEQ ID NO: 3), as claimed in claim 2, for more efficient expression in *E. coli*, and practice the subject mater as claimed without undue experimentation.

Applicants' argument has been fully considered but has not been found to be persuasive.

The instant claims are directed to a modified DNA sequence encoding hG-CSF, an expression plasmid comprising same, and a process of constructing the DNA sequence, comprising a nucleotide sequence having at least the following sequence segments, modified with respect to a native sequence of hG-CSF (SEQ ID NO: 3):

a "segment I" (located at the 5' terminal end of the native hG-CSF sequence between nucleotide positions 3 and 194, comprising replacements selected from the group consisting of replacements of *E. coli* rare codons by *E. coli* preference codons, replacements of GC rich regions by AT rich regions, and combinations thereof;

a "segment II" (located between nucleotide positions 194 and 309 of the native hG-CSF sequence), comprising replacements of *E. coli* rare codons by *E. coli* preference codons;

a "segment III" (located between nucleotide positions 309 and 467 of the native hG-CSF sequence), comprising replacement of a CGG Arg148 codon with a CGT Arg148 codon and replacement of a GGA Gly150 codon with a GGT Gly 150 codon; and

a "segment IV" (located at the 3' terminal end of the native hG-CSF sequence, between nucleotide positions 467 and 536), comprising replacements of *E. coil* rare codons by *E. coli* preference codons;

wherein the DNA sequence further comprises a 5'-UTR of the native hG-CSF sequence; and wherein the DNA sequence encodes a biologically active G-CSF, and provides an expression level of G-CSF, to the total proteins after expression, of at least 50% in an expression system, as quantified by staining protein bands after separation by SDS-PAGE.

The claims encompass a genus of molecules, *i.e.,* modified DNA sequences for hG-CSF that contain replacements of multiple *E. coli* rare codons with *E. coli* preference codons, replacements of GC rich regions by AT rich regions, and combinations thereof, throughout the gene, wherein these DNA sequences, when expressed in *E. coli*, can produce hG-CSF at a level >50% of total protein. Applicant has provided a single species, Fopt5 of SEQ ID NO: 1, which includes codon-optimization at numerous positions throughout the gene, and which is a high yield producer in *E. coli* (pp. 19, Table 1, and pp. 21, Table 2). Applicant, however, has not provided adequate written description and evidence of possession of the claimed genus, and the specification has not provided sufficient distinguishing identifying characteristics of the genus. While Applicant lists positions that may be changed, e.g., on pages 9-10 of the specification, however, there is not adequate teachings as to where and what changes are required and sufficient so that the DNA sequence would produce the protein with a high yield, i.e., at least 50% of total protein after expression. It should be noted that the nucleotide sequence of SEQ ID NO: 1 has 77.1% homology with the wild-type human G-CSF (see sequence alignment attached), suggesting a large number of nucleotide changes are required for a high producer. Disclosure of a single species of Fopt5 (SEQ ID NO: 1) is

not sufficient to define the characteristics of all modified hG-CSF genes encompassed in the claims, because it fails to teach the correlation of structure to function. MPEP 2163 states: a biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

For these reasons, the specification does not provide adequate written description of the claimed genus.

Claims 2-5, 7, 15-19 and 26 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: *a modified DNA sequence coding for hG-CSF, comprising the nucleotide sequence of SEQ ID NO: 1, wherein the DNA sequence provides an expression level of hG-CSF of at least 50% to the total proteins,* does not reasonably provide enablement for other modified hG-CSF DNA sequences (or synthetic genes), which comprises various nucleotide changes as recited in claim 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention

commensurate in scope with these claims. The basis for this rejection has been set forth in the previous office action.

Applicant argues that the specification fully describes how to optimize the native gene coding for hG-CSF, defined by SEQ ID NO: 3, by making modifications to particular segments of the gene, as taught on pages 8-10 of the specification. Applicant argues that the specification has provided an example of how to make a particular optimized gene, Fopt5, described by SEQ ID NO: 1, and it is believed a person of skill in the art could readily apply the concepts described in the specification to further optimize the native gene (SEQ ID NO: 3), as claimed in claim 2, for more efficient expression in *E. coli*, and practice the subject mater as claimed without undue experimentation.

Applicants' argument has been fully considered but has not been found to be persuasive.

As stated above, the claims encompass a large genus of molecules, *i.e.,* modified DNA sequences of hG-CSF, defined by SEQ ID NO: 3, wherein the modifications include replacements of multiple *E. coli* rare codons with *E. coli* preference codons, replacements of GC rich regions by AT rich regions, and combinations thereof, throughout the gene. The claims require that these genes, when expressed in *E. coli*, can produce hG-CSF at a level >50% of total protein. While the specification provides a list of codon positions that may be optimized (pp. 9-10), however, the specification has not provided supporting evidence that the genus of the DNA sequences can produce the high yield when expressed in *E.coli*, nor provided sufficient guidance as to which codon changes are required and sufficient to achieve the

high yield production. All that provided is one single species, a codon-optimized Fopt5 synthetic gene (SEQ ID NO: 1), which can achieve a high yield of hG-CSF (> 40% of total protein) (pp. 19, Table 1, and pp. 21, Table 2). This single species, however, is not sufficient disclosure for the genus, because it fails to provide guidance as to what other combination(s) of codon optimization can be made so that the resulting DNA sequences would produce a high protein yield. As discussed in the previous office action, while incorporating silent mutations by using *E. coli* preferred codon usage have been demonstrated to improve the level of heterologous protein expression in *E. coli*, however, codon sequence alterations do not always lead to an increase in the levels of protein expression. Further, the art (Krishna Rao et al., the reference provided previously) has shown that there is a significant variation of the expression levels for codon-optimized rhG-CSF genes (Table 1), and that alterations of codon usage at different positions, as well as N-terminal (2-10 codons) AT content, have a significant impact on the G-CSF expression efficiency. Identifying the effects of these different positions, as well as nearly infinite number of combinations of codon positions, requires a tremendous quantity of experimentation, which is undue. Even the specification provides an assay for testing a modified DNA sequence for expression level, however, the enablement requirement of 35 U.S.C. 112, first paragraph stipulates one of ordinary skill in the art to make and use the invention, rather than "make and test".

In the absence of the supporting evidence that the genus of synthetic hG-CSF genes can act in a similar manner as Fopt5 to produce the required high protein yield, and without sufficient guidance for the correlation of structure to function, one of skill in

the art would evaluate an extremely large number of non-exemplified synthetic hG-CSF genes, and determine the effects of different codon optimizations on expression yield. Thus, undue experimentation would be required for the artisan to make and use the invention as broadly claimed.

Claim Objections

Claims 25 and 26 are objected to because of the following informalities:

It is noted that the claim identifiers for claims 25 and 26 are incorrect. Claims 25 and 26 should be indicated as "Previously Presented" rather than "New". Future responses must include the proper claim identifier.

Appropriate correction is required.

Conclusion

CLAIMS 1, 6, 8-11, 13, 14 AND 20-22 ARE ALLOWABLE.

CLAIM 25 IS OBJECTED.

CLAIMS 2-5, 7, 15-19 and 26 ARE REJECTED.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
January 16, 2009

/Elizabeth C. Kemmerer/
Elizabeth C. Kemmerer, Ph.D.
Primary Examiner, Art Unit 1646